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RESEARCH ARTICLE

Neurodevelopmental outcomes at 2 years in children who received sildenafil therapy in utero: The STRIDER randomised controlled trial

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Abstract

Objective: Severe early-onset fetal growth restriction (FGR) causes stillbirth, neonatal death and neurodevelopmental impairment. Poor maternal spiral artery remodelling maintains vasoactive responsiveness but is susceptible to treatment with sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, which may improve perinatal outcomes.

Design: Superiority, double-blind randomised controlled trial.

Setting: A total of 20 UK fetal medicine units.

Population: Pregnancies affected by FGR, defined as an abdominal circumference below the tenth centile with absent end-diastolic flow in the umbilical artery between 22^{+0} and 29^{+6} weeks of gestation.

Methods: Treatment with sildenafil (25 mg three times/day) or placebo until delivery or 32 weeks of gestation.

Main outcome measures: All infants alive at hospital discharge were assessed for cardiovascular function and cognitive, speech/language and neuromotor impairment at 2 years of age. The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley-III composite score of >85.

Results: In total, 135 women were randomised between November 2014 and July 2016 (70 to sildenafil and 65 to placebo). We previously published that there was no

Study registration: ISRCTN, ISRCTN39133303; EudraCT, 2013-005398-32; MHRA CTA, 04196/0032/001-0001; REC, 14/NE/0011 (phase 1) and 16/LO/2225 (phase 2).

improvement in time to delivery or perinatal outcomes with sildenafil. In all, 75 babies (55.5%) were discharged alive, with 61 infants eligible for follow-up (32 sildenafil and 29 placebo). One infant died (placebo), three mothers declined and ten mothers were uncontactable. There was no difference in neurodevelopment or blood pressure following treatment with sildenafil. Infants who received sildenafil had a larger head circumference at 2 years of age (median difference 49.2 cm, IQR 46.4–50.3, vs 47.2 cm, 95% CI 44.7–48.9 cm).

Conclusions: Sildenafil therapy did not prolong pregnancy or improve perinatal outcomes and did not improve infant neurodevelopment in FGR survivors. Therefore, sildenafil should not be prescribed for this condition.

KEYWORDS

birthweight, fetal growth restriction, infant, neurodevelopment, newborn, placenta, pregnancy, sildenafil citrate

1 | INTRODUCTION

Severe early-onset fetal growth restriction (FGR) is associated with stillbirth,[1,2] neonatal death and prolonged neonatal admission.[3] Currently, there is no effective treatment for FGR, with elective preterm delivery the only management option. FGR poses the dilemma of choosing early delivery with prematurity or risking intrauterine death secondary to critical fetal hypoxia.[4].

Being born too small and too early can pose significant health risks throughout a child's life. In particular, FGR has adverse effects on brain structure and function, which are independent of gestational age at birth,[5] often compounded by poor postnatal growth, ultimately leading to an increased risk of neurological impairment, cognitive impairment, inattention, and specific difficulties with executive functions and impulsivity.[6]

Between 25% and 40% of surviving growth-restricted infants born very preterm have developmental impairment,[7,8] in particular in the areas of fine and gross motor function, attentional performance,[5] and language,[9] and with a mean difference in Full Scale IQ of almost 1 SD by the time they reach school age, compared with preterm and term appropriate for gestational age (AGA) controls.[10,11] In addition, FGR is a well-recognised risk factor for later life diseases, such as hypertension, diabetes and ischaemic heart disease,[12] linked to increased arterial stiffness and aortic wall thickening.[13,14]

Fetal growth restriction (FGR) often occurs secondary to abnormal placental development and a failure to remodel the maternal vessels, leading to the retention of their muscular layer and, therefore, their responsiveness to nitric oxide (NO).[15] Therefore, sildenafil, an inhibitor of phosphodiesterase type 5 (PDE5) potentiates the effect of NO and has the potential to increase uteroplacental circulation and perfusion.

In animal models, sildenafil has shown promise to improve placental function and infant growth,[15–17] in the treatment of pre-eclampsia,[18,19] and as an agent for improving fetal growth.[18,20,21] We set out to investigate whether oral treatment with sildenafil was effective in reducing poor outcomes in early-onset FGR. This study comprised a randomised controlled trial with the primary outcome of a 1 week prolongation of pregnancy and a 2 year follow-up phase to assess neurological impairment and behaviour.[22] However, prolonging the time that the fetus remains within a hostile uterine environment could lead to worse long-term outcomes for the infant. Here we present the 2-year infant outcome data from the UK STRIDER trial.

2 | METHODS

2.1 | Study design and participants

Participants were recruited from 19 UK tertiary obstetric units with a high standard of fetal medicine and neonatal services.

Women with a singleton pregnancy between 22^{+0} and 29^{+6} weeks of gestation, confirmed by first-trimester ultrasound, with a diagnosis of severe early-onset FGR and a plan for expectant management were eligible for inclusion. FGR was defined as a fetus with an estimated fetal weight (EFW) or abdominal circumference (AC) below the tenth centile using local charts and absent or reversed end-diastolic flow (EDF) in the umbilical artery (UA) on Doppler velocimetry. We excluded women from the study if they were less than 16 years of age, had a known contraindication to sildenafil, used cocaine, had a known or suspected significant chromosomal or structural anomaly, or were likely to need delivery within 72 h (e.g. with severe pre-eclampsia).

Ethical approval for this follow-up study was given by the North East Research Ethics Committee (14/NE/0011) in the UK. Each participating site provided site-specific approval and all participants provided written informed consent. An Independent Safety Data Monitoring Committee (ISDMC) was established to review the safety and efficacy data. The trial protocol was first registered on 31 July 2014, 4 months prior to the first participant being recruited (ISRCTN 39133303).

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2.2 | Randomisation and masking

We used a web-based application to allocate treatment (1 : 1) with randomisation stratification by site and gestation ($<26^{+0}$ and $\geq 26^{+0}$ weeks of gestation).

A full history was taken, measurements of maternal cardiovascular parameters (blood pressure and pulse rate), fetal biometry and Doppler velocimetry were performed and maternal venepuncture for angiogenic bloods was undertaken.

Participants were reviewed 2 h after receiving the first dose, at 3–4 days after the first dose and at least weekly thereafter. The remainder of clinical care was conducted at the discretion of the local fetal medicine experts and included regular ultrasound assessment of growth and Doppler and antenatal cardiotocography. Criteria for delivery were not dictated by the study protocol but were expected to follow the Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) study protocol.[4]

Study medication was over encapsulated (Sharp Clinical Services, Crickhowell, UK) to ensure that participants, clinicians and pharmacists were blinded to the study drug.[22] Medication was dispensed in 10-day supplies with a new supply being provided weekly to ensure that there was no period where medication was missed. All participants received oral sildenafil at a dose of 25 mg, three times per day, or placebo prescribed orally. This dosage regimen was determined by previous studies.[18,20] Pharmacy logs were used to determine adherence. Treatment ended at 31^{+6} weeks of gestation or delivery, whichever came first. All participants were advised of the potential side effects of the medication.

Data regarding pregnancy outcomes were collected prospectively from clinical maternity notes and entered onto a secure electronic case report form (eCRF) platform at the research sites. Data quality and protocol compliance was monitored regularly with central and on-site monitoring methods.

2.3 | Outcome measures

The primary outcome measure was time from randomisation to delivery, measured in days, which has previously been reported.[22] This pragmatic design relied upon an assumption that an increase in survival would be clinically significant if sildenafil were able to prolong pregnancy by 1 week.

The follow-up component aimed to assess all babies alive at discharge for cardiovascular function, neuromotor impairment, and cognitive, speech/language and motor development at 2 years of age. The primary outcome was survival without cerebral palsy or neurosensory impairment, or a Bayley-III composite score of >85, but was not powered for this outcome as it was based on survivors.

All surviving infants of mothers recruited to the STRIDER study were eligible and invited for follow-up. A study invitation pack was sent to all parents/carers of surviving children. This included an invitation letter, a participant information sheet and an informed consent form. Participants who did not contact the research team within 2 weeks were contacted by a member of the research team.

Assessments took place in a clinical research setting or in the child's home. Informed written consent was obtained before the assessment began. All assessments were performed by a single senior research psychologist with expertise in developmental assessment techniques. This researcher was blinded to treatment allocation.

Assessments included the cognitive, language and motor subscales of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III),[23,24] and Hempel's Neurological Examination for Toddler Age,[25] to identify major neurological impairment (i.e. cerebral palsy, CP) and subtle deviations from typical neurological and neuromotor function.[26] In addition, a cardiovascular assessment was undertaken, which included brachial systolic blood pressure (BP) and diastolic BP and arterial stiffness, assessed with the aortic (central) augmentation index (AIx).

Where potential participants cancelled or failed to attend follow-up appointments on more than three occasions, they were invited to participate remotely. All such participants received a follow-up questionnaire pack, which included a participant information sheet, a consent form and all questionnaires assigned to the main study, in addition to the Ages and Stages Questionnaire 3 (ASQ-3), in place of the BSID-III neurodevelopmental assessment.[27].

The Health Status Classification System – Preschool Version (HSCS-PS) is a parental (or clinician) proxy measurement of the health status of a child. The overall health status is described as a ten-element vector consisting of one level for each domain. In this study, to facilitate comparisons between groups, a total 'quality of health score' for the overall health state of a child was calculated as the sum of the level codes for the original domains. Therefore, the range of the disability score varied from 10 (no disability in any domain) to 41 (maximum disability in all ten domains).[28]

The Child Behaviour Checklist (CBCL 1.5–5) was used to assess emotional and behavioural difficulties. Raw scores are normalised into *t*-scores (mean 50, SD 10).[29] Higher *t*-scores represent more problematic behaviour: *t*-scores below 60 are in the normal range; *t*-scores of 60–63 (84th–90th percentile) are in the borderline range; and *t*-scores above 63 (above 90th percentile) are in the clinical range. The *t*-scores are dichotomised into typical (scores in the normal range) and atypical (scores in the borderline and clinical range).[29]

The Behaviour Rating Inventory of Executive Function – Preschool (Brief-P) is a parent questionnaire for the early assessment of executive function, and assesses the severity of executive dysfunction in day-to-day situations.[30] Age-based *t*-scores are computed for each subscale and index, and a score of 65 or higher is considered a clinically significant problem.

2.4 | Adverse events and adherence

We assessed and recorded adverse events at weekly clinical reviews from recruitment to delivery. Participants were encouraged to report side effects or adverse events. We assessed adherence during the weekly clinical reviews and considered adherence to treatment to be good if the reported intake of medication was 90% or more of the total expected to have been taken up to this point.

2.5 | Statistical analysis

Participant groups for analysis were defined on an intention-to-treat (ITT) basis. As the primary outcome is a measure of time, Kaplan–Meier estimates are provided to summarise the data. As there are no censored observations, standard linear regression techniques are used to analyse the data. Analyses were stratified by gestation period but not by site, owing to the low numbers of patients at each site. The treatment effect was reported as the mean difference between groups. Statistical significance was determined as $P \leq 0.05$, and participants randomised at $<26^{+0}$ and $\geq 26^{+}0$ weeks of gestation were included in the subgroup analyses.

For continuous data, the analysis of secondary end points matched the analysis for the primary end point. Binary data were compared across treatment groups using a chi-square (χ^2) test or Fisher's exact test, as appropriate, and reported using risk ratios (RRs) with 95% confidence intervals (95% CIs). All analyses were performed using the statistical software package R 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

2.6 | Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the article. RJ, CC, AS and ZA had full access to the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

3 | RESULTS

We recruited 135 participants between 21 November 2014 and 6 July 2016: 75 participants were recruited before 26^{+0} weeks of gestation and 60 participants were recruited between 26^{+0} and 29^{+6} weeks of gestation; 70 participants were randomly assigned to receive sildenafil and 65 participants were randomly assigned to receive placebo. None of the participants either withdrew their consent or were lost to follow-up prior to delivery; therefore, additional 'per protocol' analysis was not performed. The follow-up phase was able to assess 81% of eligible participants at 2 years of age. Out of 75 babies who were discharged alive from the neonatal unit, 61 infants (81.3%) were included in the follow-up phase. Of those not followed up, one infant died (placebo), three mothers declined follow-up and ten mothers were uncontactable. This left the infants of 32 mothers who had received sildenafil and 29 mothers who had received placebo for assessment in the follow-up phase (Figure 1; Table S1).

Differences at baseline were not clinically important between the sildenafil group and the placebo group, and were reported in our previous article.[22] The median gestation at randomisation was 24.4 weeks (IQR 24.0–27.5 weeks). Two babies were diagnosed postnatally with trisomy 21 (Down

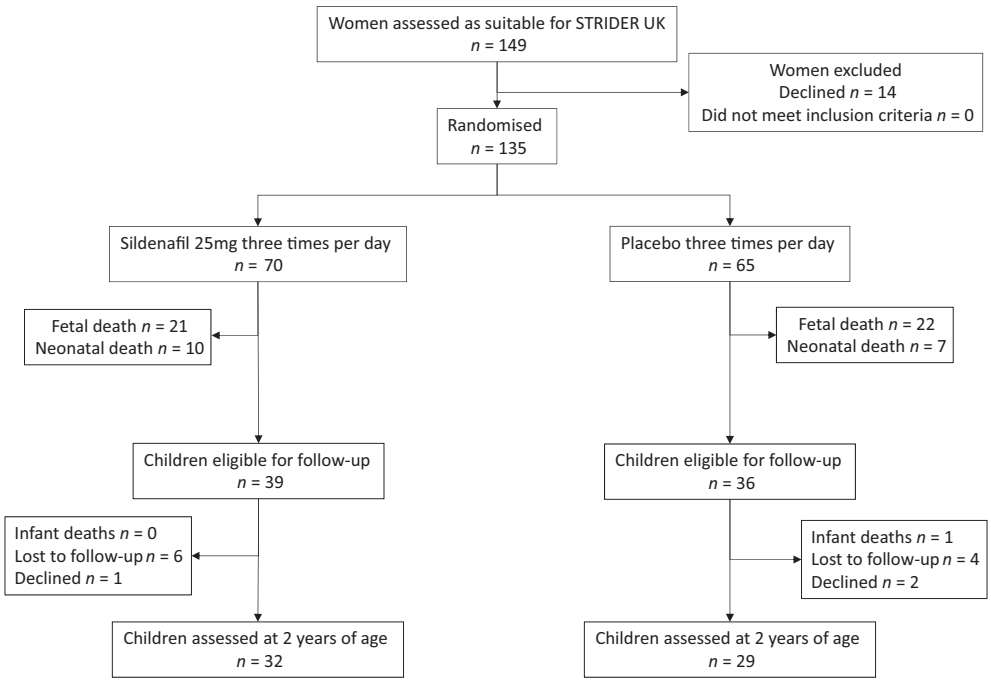

FIGURE 1 Flow chart of the STRIDER UK study.

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syndrome) (one sildenafil and one placebo) and two had confirmed cytomegalovirus infection (one sildenafil and one placebo); all four babies were included in the ITT analysis.[22] There was no beneficial effect on maternal cardiovascular function from treatment with sildenafil.[31]

The follow-up phase was delayed because of the impact of the Covid-19 pandemic on research staff availability and access to patients. There was no difference in the sex, birthweight, gestation at delivery (median 29.2 vs 29.9 weeks of gestation), mode of delivery or oxygen usage between the two groups (Table 1).

The physical characteristics of the population are shown in Table 2. There were no differences between the groups in height or weight. The head circumference was slightly larger in children of mothers treated with sildenafil (median 49.25 cm, IQR 46.43–50.26 cm) versus placebo (median 47.18 cm, IQR 44.71–48.95 cm). There were no differences for systolic and diastolic BP between children of mothers treated with sildenafil and children of mothers treated with placebo. The median values were appropriate for children aged 2 years. The proportion of infants without CP was 22/26 (85%) in the group treated with sildenafil and 19/24 (80%) in the group treated with placebo (Table 3).

The BSID-III assessment showed no meaningful differences in cognitive, language (including receptive and expressive language) or motor (including fine and gross motor) subscales between children born to sildenafil- and placebo-treated mothers (Table 3). The total scores were somewhat lower than expected across all three domains, compared

TABLE 1 Follow-up infant demographics.

Covariate	Sildenafil $n = 32$	Placebo $n = 29$	Relative risk (95% CI)
Gestation at birth (weeks)			
Median (IQR)	29.21 (28.07–30.28)	29.85 (28.42–31)	–
Mode of delivery			
Emergency caesarean section	12 (38%)	8 (28%)	1.36 (0.65–2.85)
Prelabour caesarean section	18 (56%)	21 (72%)	0.78 (0.53–1.14)
Vaginal	2 (6%)	0 (0%)	–
Sex of child			
Female	12 (38%)	11 (38%)	0.99 (0.60–1.62)
Birthweight (g)			
Median (IQR)	750 (597.5–945.75)	800 (610–1000)	–
Oxygen dependency at 28 days			
Yes	16 (50%)	11 (38%)	1.32 (0.74–2.36)
Oxygen dependency at 36 weeks			
Yes	9 (28%)	4 (13%)	2.04 (0.70–5.92)
Surfactant use			
Yes	24 (75%)	16 (55%)	1.36 (0.93–1.99)
Ventilator dependency			
Yes	25	18	1.26 (0.89–1.77)

TABLE 2 Anthropometric and cardiovascular measures at age 2 years.

Covariate	Sildenafil $n = 32$	Placebo $n = 29$	Difference (95% CI)	*P*
Survivors assessed	26 (80%)	24 (83%)		
Head circumference (cm)				
Median (IQR)	49.25 (46.43–50.26)	47.18 (44.71–48.95)	2.02 (0.11, 3.93)	0.02
Height (cm)				
Median (IQR)	86.35 (83.08–90.19)	85.23 (80.95–87.65)	1.61 (−1.06, 4.29)	0.30
Weight (kg)				
Median (IQR)	10.53 (9.80–11.77)	10.08 (9.30–11.61)	0.34 (−0.63, 1.32)	0.37
Systolic blood pressure (mmHg)				
Median (IQR)	95.25 (90.75–104.63)	100.25 (91.38–107.38)	−3.18 (−9.07, 2.72)	0.38
Diastolic blood pressure (mmHg)				
Median (IQR)	60 (58.50–62.88)	62.25 (58.13–65.13)	−0.94 (−4.02, 2.14)	0.43

with standard population norms (i.e. 100, SD 15); however, the difference was neither clinically nor statistically significant. There was no difference between the sildenafil and placebo groups for the presence of CP reported by parents.

Functional assessment with the BRIEF-P (Table 4) demonstrated no difference in adjusted *t*-scores between sildenafil and placebo for any of the domains assessed. Likewise, the median total CBCL 1.5–5 scores and adjusted *t*-scores (Table 5) also showed no difference between infants whose mothers were treated with sildenafil versus placebo for any of the domains assessed.

The HSCS scores are shown as a total score by domain and as individual components (Table 6). There was no difference

TABLE 3 Child Neurodevelopmental Assessment at age 2 years.

Covariate	Sildenafil *n* = 32	Placebo *n* = 29	RR (95% CI)	*P*
Survivors assessed for neurodevelopment	26 (80%)	24 (83%)	–	–
CP				
Yes	4 (15%)	5 (21%)	0.64 (0.72, 1.22)	0.721
BSID-III cognitive, composite score				
Median (IQR)	92.5 (90–103.75)	90 (80–100)	5.85 (−1.87, 13.57)	0.139
BSID-III cognitive, <85				
Yes	3 (12%)	8 (33%)	0.75 (0.55, 1.03)	0.091
BSID-III cognitive, <85 & CP				
Yes	1 (4%)	3 (12%)	0.91 (0.77, 1.08)	0.34
BSID-III language, composite score				
Median (IQR)	89 (86–91)	86 (78.5–91)	3.19 (−3.17, 9.54)	0.352
BSID-III language, <85				
Yes	5 (19%)	9 (38%)	0.77 (0.53, 1.11)	0.211
BSID-III language, <85 & CP				
Yes	1 (4%)	5 (21%)	0.82 (0.66, 1.03)	0.093
BSID-III motor, composite score				
Median (IQR)	88 (82, 94)	91 (84.25, 100)	−1.22 (−8.84, 6.39)	0.507
BSID-III motor, <85				
Yes	8 (31%)	6 (25%)	1.08 (0.77, 1.53)	0.757
BSID-III motor, <85 & CP				
Yes	3 (12%)	4 (17%)	0.94 (0.75, 1.18)	0.697

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CP, cerebral palsy; RR, risk ratio.

TABLE 4 Sum of scores and *t*-scores across Behaviour Rating Inventory of Executive Function – Preschool BRIEF-P domains.

	Sildenafil *n* = 32	Placebo *n* = 29	RR (95% CI)	*P*
Inhibit				
Sum	1 (0, 2.75) [0, 5]	1 (0, 3) [0, 14]	−0.64 (−3.29, 2.01)	0.826
t-score	49 (48, 52) [24, 54]	51 (50, 53) [50, 60]	1 (−8, 10)	
Shift				
Sum	4 (2, 6) [0, 14]	4 (2.75, 9) [0, 19]	−1.01 (−3.24, 1.21)	0.561
t-score	53 (51, 56) [48, 66]	53 (52,59) [48,73]	1 (−3, 5)	
Emotional control				
Sum	3 (0.5, 7) [0, 16]	3 (2, 10.25) [0, 17]	−1.46 (−4.05, 1.13)	0.391
t-score	53 (50, 58) [50, 70]	53 (52,62) [50, 71]	0 (−3, 4)	
Working memory				
Sum	8 (4, 15) [1, 26]	10.5 (3, 14) [0, 27]	−1.08 (−4.99, 2.83)	0.600
t-score	55 (52, 59) [51, 65]	56 (52, 58) [50, 65]	1 (−3, 5)	
Plan/organise				
Sum	3 (1, 6.5) [0, 15]	4 (2, 6) [0, 16]	0.17 (−2.01, 2.35)	0.813
t-score	53 (51, 57) [50, 66]	54 (51, 56) [50,67]	1 (−6, 7)	

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TABLE 5 Sum of scores and *t*-scores across Child Behaviour Checklist CBCL 1.5–5 domains.

	Sildenafil	Placebo	RR (95% CI)	*P*
Emotionally reactive				
Sum	1 (0, 2.75) [0, 5]	1 (0, 3) [0, 14]	−0.54 (−1.81, 0.73)	0.700
t-score	50 (50, 54) [50, 62]	50 (50, 55) [50, 87]	−0.28 (−1.53, 0.98)	
Anxiety/Depression				
Sum	1.5 (0, 3) [0, 7]	2 (0.75, 2.25) [0, 12]	0.02 (−1.12, 1.15)	0.594
t-score	50 (50, 51) [50, 66]	50 (50, 50.25) [50, 74]	−0.52 (−1.85, 0.81)	
Somatic complaints				
Sum	1.5 (1, 3.75) [0, 9]	2 (1, 3) [0, 8]	−0.39 (−1.67, 0.89)	0.941
t-score	51.5 (50, 61) [50, 74]	53 (50, 58) [50, 72]	0.18 (−1.08, 1.44)	
Withdrawn				
Sum	1 (0, 2.75) [0, 7]	1 (1, 2.5) [0, 14]	0.93 (−2.19, 4.05)	0.472
t-score	51 (50, 59) [50, 73]	51 (51, 57.75) [50, 94]	−1.45 (−4.71, 1.81)	
Sleep problems				
Sum	1 (0, 2.75) [0, 10]	2 (0, 3.25) [0, 10]	−0.3 (−2.97, 2.36)	0.405
t-score	50 (50, 52.5) [50, 76]	51 (50, 53.75) [50, 76]	0.16 (−3.43, 3.74)	
Attention problems				
Sum	3 (1, 5) [0, 7]	2 (1, 4) [0, 10]	−1.22 (−5.68, 3.25)	0.384
t-score	53 (50, 62) [50, 70]	51 (50, 57) [50, 80]	−0.77 (−3.82, 2.28)	
Aggressive behaviour				
Sum	7.5 (5.25, 12) [0, 23]	6 (3, 11.5) [0, 19]	0.04 (−3.8, 3.88)	0.333
t-score	51 (51, 53) [50, 68]	51 (50, 53) [50, 63]	0.32 (−2.01, 2.66)	
Internalising				
Sum	5 (3, 11.5) [0, 27]	6 (4.5, 9.5) [0, 41]	−0.54 (−1.81, 0.73)	0.602
t-score	52 (50.312, 55.94) [50, 68]	51.8 (51, 54.8) [50, 76.2]	−0.28 (−1.53, 0.98)	
Externalising				
Sum	10 (6.25, 16.75) [0, 28]	7 (4, 16) [0, 26]	0.02 (−1.12, 1.15)	0.287
t-score	52 (50.5, 56.875) [50, 65]	51 (50, 55.25) [50, 69.5]	−0.52 (−1.85, 0.81)	

between infants who had received sildenafil and those who had received placebo for any of the domains assessed.

It was not possible to record the Hempel assessments and, as such, direct neurological assessments could not be made. However, we were able to obtain information on neurology from the medical notes and there was no difference in the incidence of CP between the sildenafil group ($n = 4$) and the placebo group ($n = 5$).

Unfortunately, no infants were able to remain calm and relaxed during the non-invasive cardiac output monitor (NICOM) cardiovascular test, leaving blood pressure as the sole assessment of infant cardiovascular status.

4 | DISCUSSION

4.1 | Principal findings

The results of the STRIDER study demonstrated that sildenafil did not result in the prolongation of pregnancy, or to improvements in fetal growth or perinatal outcome, when administered to pregnant women with a severely growth-restricted fetus.[22] These results have subsequently been confirmed in a number of other studies.[32–34]

Our study demonstrated a lack of benefit on any neurodevelopmental, emotional or behavioural assessment from treatment with sildenafil, although the study was only powered for short-term perinatal outcomes and so caution should be exercised in interpreting this neurodevelopmental result.

4.2 | Results

This study defines the impact of antenatal treatment with sildenafil in women with severe early-onset FGR on the well-being of their infants at 2 years of age. Previously we showed no benefit to the prolongation of pregnancy or perinatal outcomes.[22] This study now confirms the ineffectiveness of this treatment to improve longer-term outcomes in infants with severe early-onset FGR and is supportive of a similar study recently published from Australia and New Zealand.[35]

TABLE 6 Health Status Classification System-Preschool (HSCS-PS) individual domains.

		Answer				
Question	**Treatment**	**0**	**1**	**2**	**3**	**4**
Vision_a	Placebo ($n=28$)	3 (11%)	23 (82%)	2 (7%)	0 (0%)	0 (0%)
	Sildenafil ($n=30$)	6 (20%)	22 (73%)	2 (7%)	0 (0%)	0 (0%)
	Total ($n=58$)	9 (16%)	45 (78%)	4 (7%)	0 (0%)	0 (0%)
Vision_b	Placebo ($n=28$)	2 (7%)	24 (86%)	1 (4%)	0 (0%)	1 (4%)
	Sildenafil ($n=30$)	3 (10%)	25 (83%)	2 (7%)	0 (0%)	0 (0%)
	Total ($n=58$)	5 (9%)	49 (84%)	3 (5%)	0 (0%)	1 (2%)
Hearing	Placebo ($n=28$)	0 (0%)	26 (93%)	1 (4%)	1 (4%)	0 (0%)
	Sildenafil ($n=29$)	1 (3%)	27 (93%)	1 (3%)	0 (0%)	0 (0%)
	Total ($n=57$)	1 (2%)	53 (93%)	2 (4%)	1 (2%)	0 (0%)
Speaking	Placebo ($n=28$)	0 (0%)	8 (29%)	10 (36%)	9 (32%)	1 (4%)
	Sildenafil ($n=30$)	0 (0%)	7 (23%)	15 (50%)	6 (20%)	2 (7%)
	Total ($n=58$)	0 (0%)	15 (26%)	25 (43%)	15 (26%)	3 (5%)
Mobility	Placebo ($n=28$)	0 (0%)	21 (75%)	6 (21%)	1 (4%)	0 (0%)
	Sildenafil ($n=30$)	1 (3%)	19 (66%)	8 (28%)	1 (3%)	0 (0%)
	Total ($n=58$)	1 (2%)	40 (70%)	14 (25%)	2 (4%)	0 (0%)
Dexterity	Placebo ($n=28$)	0 (0%)	24 (86%)	4 (14%)	0 (0%)	0 (0%)
	Sildenafil ($n=30$)	1 (3%)	19 (63%)	8 (27%)	1 (3%)	1 (3%)
	Total ($n=58$)	1 (2%)	43 (74%)	12 (21%)	1 (2%)	1 (2%)
Self-care	Placebo ($n=28$)	0 (0%)	15 (54%)	6 (21%)	5 (18%)	2 (7%)
	Sildenafil ($n=30$)	1 (3%)	15 (50%)	11 (37%)	3 (10%)	0 (0%)
	Total ($n=58$)	1 (2%)	30 (52%)	17 (29%)	8 (14%)	2 (3%)
Emotion	Placebo ($n=28$)	0 (0%)	20 (71%)	6 (21%)	2 (7%)	0 (0%)
	Sildenafil ($n=30$)	1 (3%)	22 (73%)	7 (23%)	0 (0%)	0 (0%)
	Total ($n=58$)	1 (2%)	42 (72%)	13 (22%)	2 (3%)	0 (0%)
Learning and remembering	Placebo ($n=28$)	0 (0%)	17 (61%)	8 (29%)	3 (11%)	0 (0%)
	Sildenafil ($n=30$)	1 (3%)	20 (67%)	8 (27%)	1 (3%)	0 (0%)
	Total ($n=58$)	1 (2%)	37 (64%)	16 (28%)	4 (7%)	0 (0%)
Thinking and problem-solving	Placebo ($n=28$)	0 (0%)	11 (39%)	12 (43%)	2 (7%)	3 (11%)
	Sildenafil ($n=30$)	1 (3%)	16 (53%)	10 (33%)	3 (10%)	0 (0%)
	Total ($n=58$)	1 (2%)	27 (47%)	22 (38%)	5 (9%)	3 (5%)
Pain and discomfort	Placebo ($n=28$)	0 (0%)	19 (68%)	8 (29%)	1 (4%)	0 (0%)
	Sildenafil ($n=30$)	0 (0%)	26 (87%)	4 (13%)	0 (0%)	0 (0%)
	Total ($n=58$)	0 (0%)	45 (78%)	12 (21%)	1 (2%)	0 (0%)
General health	Placebo ($n=28$)	0 (0%)	15 (54%)	11 (39%)	2 (7%)	0 (0%)
	Sildenafil ($n=30$)	4 (13%)	15 (50%)	11 (37%)	0 (0%)	0 (0%)
	Total ($n=58$)	4 (7%)	30 (52%)	22 (38%)	2 (3%)	0 (0%)
Behaviour	Placebo ($n=28$)	0 (0%)	20 (71%)	5 (18%)	2 (7%)	1 (4%)
	Sildenafil ($n=30$)	1 (3%)	18 (60%)	10 (33%)	1 (3%)	0 (0%)
	Total ($n=58$)	1 (2%)	38 (66%)	15 (26%)	3 (5%)	1 (2%)

4.3 | Clinical implications

Further to this lack of benefit, concerns were raised during the Dutch STRIDER trial of increased perinatal mortality in the sildenafil group.[32] Further assessment deemed this excess mortality to be predominantly the result of persistent pulmonary hypertension of the neonate (PPHN), which has been proposed to be a pathophysiological mechanism of 'rebound' vasoconstriction after the cessation of sildenafil.[36] Both the UK and the New Zealand/Australia STRIDER trials reviewed their data using the same criteria for PPHN as the Dutch STRIDER trial and did not find any increased mortality.[37]

The international STRIDER studies are committed to combining study data in a prospective individual participant data (IPD) meta-analysis to look for any possible long-term effect of sildenafil, particularly on neurodevelopmental and cardiovascular outcome.[38]

4.4 | Research implications

It is possible that future pharmacokinetic and pharmacodynamics experiments using PDE5 inhibitors may establish an efficacious therapeutic dose for FGR studies. However, on current evidence, we do not believe that there is any beneficial effect of sildenafil treatment on fetal growth, perinatal outcomes or neurodevelopment in this patient group, and would advise that further use of this drug in this population should be stopped.

4.5 | Strengths and limitations

This study is the first of its kind to report the 2-year outcomes for infants treated with sildenafil for severe early-onset FGR. The cohort represents a unique and high-risk FGR cohort managed to the highest standards within tertiary fetal medicine units within the UK. This challenging patient group represents an important addition to the literature for both sildenafil therapy and severe early-onset FGR outcomes.

Unfortunately, owing to practical limitations, we were unable to assess neurology with the Hempel test and the cardiovascular effects in the infants. Although this is a limitation in this very challenging patient group, the information obtained remains very important. The lack of cardiovascular assessment is unlikely to be critical because of the overall negative impact of sildenafil on all other parameters.

5 | CONCLUSION

The STRIDER study showed no beneficial effect for any perinatal outcome for mother or infant from treatment with 25 mg sildenafil three times daily for severe early-onset FGR. The follow-up study confirmed that there was no beneficial effect from maternal treatment with sildenafil on any behavioural assessment performed at 2 years of age in the surviving infants. There was also no effect on infant blood pressure from treatment with sildenafil.

Summary of key findings:

- sildenafil did not prolong pregnancy in severe early-onset FGR, compared with placebo
- sildenafil did not improve perinatal outcomes in severe early-onset FGR
- sildenafil did not improve maternal cardiovascular parameters in severe early-onset FGR
- sildenafil did not improve infant neurodevelopmental function at age 2 years
- sildenafil did not improve infant emotional or behavioural status at age 2 years

AUTHOR CONTRIBUTIONS

PNB conceived the idea for the study. LK, ZA, PvD, ATP and PNB developed the STRIDER study consortium. ZA and AS wrote the initial submission for funding. CC, AS and ZA wrote the submission for phase 2 funding for the study. AS, CC and ZA supervised the conduct of the randomised controlled trial. AK assessed the cardiovascular results. MAT supervised the neonatal outcomes. CC performed neurodevelopmental assessments and assessed impact with BV. JH collated the trial data. RJ performed the statistical analysis. EDJ reviewed the trial data. AS, CC, BV and ZA wrote the article. All authors reviewed the final version for publication.

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CONFLICT OF INTEREST STATEMENT

AS, CC, JH, RJ, ZA, BV, MAT and EDJ declare no conflicts of interest associated with this work. PNB and LK are minority shareholders of Metabolomic Diagnostics, a spinout company that seeks to develop screening tests for pregnancy complications. ATP is a co-founder of and shareholder of Intelligent Ultrasound, a university spinout company. AK is Vice President, Royal College of Obstetricians and Gynaecologists, and trustee of the International Society of Ultrasound in Obstetrics and Gynaecology. PvD is a shareholder in Nightingale Medical, a university spinout company.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

Ethical approval was obtained on 20 March 2014, Research Ethics Committee (REC) North East – Newcastle and North Tyneside 2, Chair Dr Alasdair MacSween (14/NE/0011, phase 1; 16/LO/2225, phase 2). Patient and public involvement (PPI) was conducted through the Antenatal Results and Choice (ARC) charity. ARC was involved with the STRIDER study from the first design stages through to the delivery of the study and the results.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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